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A mild, copper-catalysed amide deprotection strategy: use of *tert*-butyl as a protecting group



Vikki Evans, Mary F. Mahon, Ruth L. Webster*

University of Bath, Claverton Down, Bath BA2 7AY, UK

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ABSTRACT

Mild methods for the deprotection of organic substrates are of fundamental importance in synthetic chemistry. A new room temperature method using a catalytic amount of $\text{Cu}(\text{OTf})_2$ is reported. This allows use of the *tert*-butyl group as an amide protecting group. The methodology is also extended to Boc-deprotection.

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1. Introduction

The functional group protection of amines is a fundamental prerequisite in the manipulation and synthesis of a range of key organic moieties, for example, amino acids and peptides.¹ Whilst protection strategies are often mild, facile and high yielding, the corresponding deprotection should, ideally, also fulfil these requirements. Despite this, removal of common nitrogen protection groups such as Boc, tend to rely on strong acids. Although other stoichiometric² and catalytic methods are known,³ in general the reagents used are often difficult to handle and may be incompatible with other sensitive moieties that are present elsewhere in the substrate. Meanwhile, very simple functionality, for example, alkyl groups, are rarely used in protection-deprotection strategies principally because removal requires the use of strong acid and/or high temperatures,⁴ which can be detrimental to sensitive functionality elsewhere in the molecule. Reports of the use of Lewis acids to deprotect *tert*-butyl substituted tertiary amides exist.^{4g,h} However, many of the reagents are difficult to handle (SnCl_4 , TiCl_4 , $\text{ZnCl}_2 \cdot \text{OEt}_2$, $\text{BF}_3 \cdot \text{OEt}_2$, TMSOTf) and no comprehensive account of reaction conditions and substrate scope exists.

Reported herein is the use of the *tert*-butyl group as an amide *N*-protecting species, which undergoes mild, catalytic cleavage with $\text{Cu}(\text{OTf})_2$. To the best of our knowledge this is the first catalytic report of de-*tert*-butylation. The reaction has been extended to the

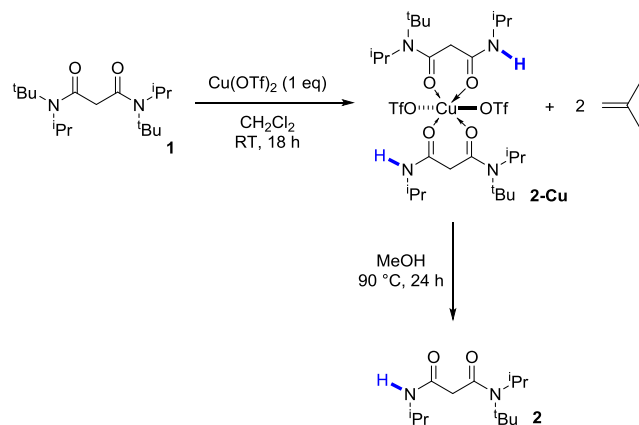
Boc group, which also shows a propensity for mild cleavage. Compared to strong acids, the use of a simple copper salt offers a very favourable set of handling conditions.

Secondary amides are important substrates, where accessing them from the tertiary precursor is an important step. For example, Shi and co-workers have used Pd-catalysed diamination to access a range of enantiopure *tert*-butyl substituted imidazolidinones,^{4e,f} where the *tert*-butyl group is removed using TFA to allow for further *N*-functionalisation. Secondary amides are also commonly used in directing group mediated catalytic C–H functionalisation.⁵ It could be envisaged that amide *N*-protection as the tertiary moiety would allow functionalisation elsewhere in the molecule, prior to mild deprotection of the *tert*-butyl group and then subsequent C–H functionalisation. This would allow the build-up molecular complexity under mild, catalytic conditions.

2. Results and discussion

During recent studies into the novel reactivity of sterically congested amides,⁶ an unusual facet of reactivity was observed.^{7,8} Upon exposure to a quantitative amount of $\text{Cu}(\text{OTf})_2$ at room temperature, bulky malonamide **1** reacts to form a new all-trans chelate, **2-Cu** (Scheme 1). X-ray diffraction shows this to be the desymmetrised malonamide, which has undergone loss of one *tert*-butyl group (Fig. 1). Further investigation shows that the *tert*-butyl is lost as isobutylene, which begins to form within minutes at room temperature: the signals corresponding to isobutylene can be clearly seen by $^{13}\text{C}\{^1\text{H}\}$ NMR.⁹ Heating the chelate in MeOH releases the pure unsymmetrical malonamide, **2**. This is a highly selective

* Corresponding author. Tel.: +44 (0) 1225 386103; fax: +44 (0) 1225 386231; e-mail address: r.l.webster@bath.ac.uk (R.L. Webster).



Scheme 1. Stoichiometric $\text{Cu}(\text{OTf})_2$ can be used to desymmetrise sterically congested malonamides within minutes at room temperature.

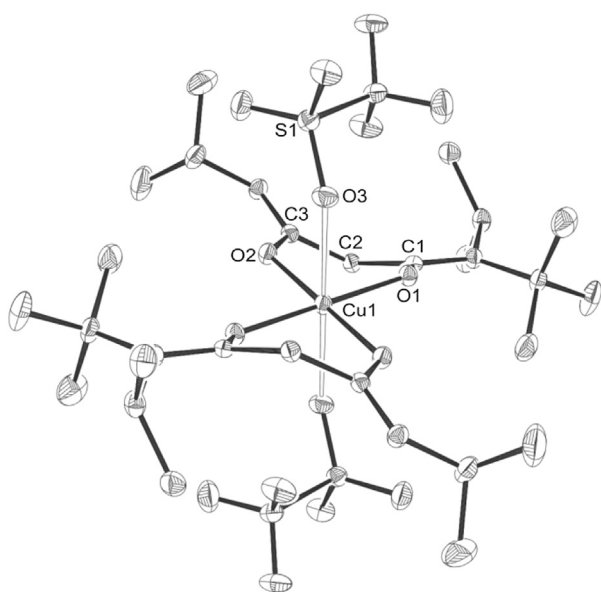


Fig. 1. Crystal structure of 2-Cu. Selected bond lengths: Cu–O1 1.945(2), Cu–O2 1.925(1), Cu–O3 2.517(2) Å. Selected bond angles: O1–Cu–O2 91.82(6), O1–Cu–O3 92.93(6), O2–Cu–O3 89.13 (6)°.

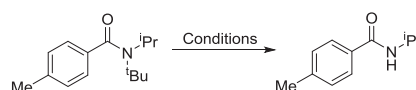
method for the desymmetrisation of malonamides and to the best of our knowledge, a selective transformation of this type has never been reported.

Wishing to explore this chemistry further, we questioned the potential of developing a $\text{Cu}(\text{OTf})_2$ -catalysed de-tert-butylation protocol. To our delight, this is indeed possible using a sterically congested amide under mild conditions with only 5 mol % copper salt (Table 1, Entry 1). The reaction proceeds at room temperature to give the de-alkylated product cleanly, in high yield and no stirring is necessary. Reactivity is only observed in the presence of triflate salts (Table 1, Entries 1 and 7–13) and is most efficient in CH_2Cl_2 and 1,4-dioxane. This is the first report of a completely air stable, room temperature, metal-catalysed method of de-tert-butylation.

We then investigated the substrate scope and noted that reducing the steric bulk around the nitrogen to an *N*-tert-butyl-*N*-ethyl amide (3a, Table 2, Entry 1) necessitates more forcing reaction conditions to remove the *tert*-butyl group (no reaction is observed after 18 h at rt but complete conversion to 3a is observed after 15 h at 50 °C). No reaction is observed with secondary *N*-tert-butylbenzamides. A range of aromatic *N*-tert-butyl-*N*-isopropylbenzamides undergo this transformation (Entries 2–6) with many proceeding with excellent yields after 18 h at rt. Sterically

Table 1

Optimisation of catalytic de-tert-butylation



Entry	Conditions	Spectroscopic yield (%) ^a
1	$\text{Cu}(\text{OTf})_2$, CH_2Cl_2	100 [82]
2	$\text{Cu}(\text{OAc})_2$, CH_2Cl_2	N.r.
3	CuCl_2 , CH_2Cl_2	N.r.
4	$\text{Zn}(\text{OAc})_2$, CH_2Cl_2	N.r.
5	ZnCl_2 , CH_2Cl_2	N.r.
6	YbCl_3 , CH_2Cl_2	N.r.
7	$\text{Bi}(\text{OTf})_3$, CH_2Cl_2	100
8	$\text{Sc}(\text{OTf})_3$, CH_2Cl_2	94
9	$\text{Cu}(\text{OTf})_2$, toluene	45
10	$\text{Cu}(\text{OTf})_2$, THF	10
11	$\text{Cu}(\text{OTf})_2$, 1,4-dioxane	92
12	$\text{Cu}(\text{OTf})_2$, EtOH	6
13	$\text{Cu}(\text{OTf})_2$, MeCN	55

Conditions: amide (0.5 mmol), metal salt (0.025 mmol, 5 mol %), solvent (5 mL), rt, 18 h.

^a Spectroscopic yield, [isolated yield]. N.r.=no reaction.

Table 2

Extent of de-tert-butylation reactivity

Starting material	Product	R/n	Yield ^a
1	3a	4a	87 ^b
2	3b	4b	H 96
3	3c	4c	4-Me 82
4	3d	4d	4-OMe 92, 94 ^c
5	3e	4e	3,5-CF ₃ 91
6	3f	4f	57 95 ^d
7	3g	4g	1 75, 95 ^d
8	3h	4h	4 74 ^d

Conditions: amide (0.5 mmol), $\text{Cu}(\text{OTf})_2$ (5 mol %), CH_2Cl_2 (5 mL).

^a Isolated yield (%).

^b 15 h, 50 °C.

^c Scale-up: 1.0 g 3d, 24 h, rt.

^d 18 h, 50 °C.

hindered naphthalenecarboxamide, 3f, requires gentle heating to enable the reaction to go to completion (Entry 6). Aliphatic amides also undergo de-tert-butylation by employing heating (Entries 7 and 8). Deprotection of tertiary amines (e.g., *tert*-butylpiperidine) does not take place and only starting material is obtained. Likewise, lactam deprotection (1-(*tert*-butyl)azetidin-2-one, 1-(*tert*-butyl)pyrrolidin-2-one and 1-(*tert*-butyl)piperidin-2-one) does not take place, even after heating to 80 °C.

Our next goal was to investigate the applicability to Boc-deprotection (Table 3). Again, mild cleavage is observed across a range of benzamide substrates (Entries 1–3), whilst deprotection of an aliphatic substrate (Entry 5) and common lactam motifs (Entries 6–9) under gentle heating (50 °C) is possible. Intrigued by the possibility of selectively removing a *tert*-butyl group in the presence of a Boc group, we synthesised a sterically congested *N*-

Table 3
Extent of Boc-deprotection reactivity

Starting material	Product	R/n	Yield ^a	
1	5a	4b	H	73
2	5b	4c	4-Me	77
3	5c	4d	4-OMe	80
4	5d	4f		73
5	5e	4h	4	64, 94 ^b
6	5f	6a	1	94 ^b
7	5g	4k	2	95 ^b
8	5h	6b	3	54 ^b
9	5i	6c		83
10	5j	6d		39 ^c
11	5k	6e		82
12	5l	6f		90
13	5m	6g		96

Conditions: amide (0.5 mmol), Cu(OTf)₂ (5 mol %), CH₂Cl₂ (5 mL).^a Isolated yield (%).^b 18 h, 50 °C.^c 18 h, 80 °C.

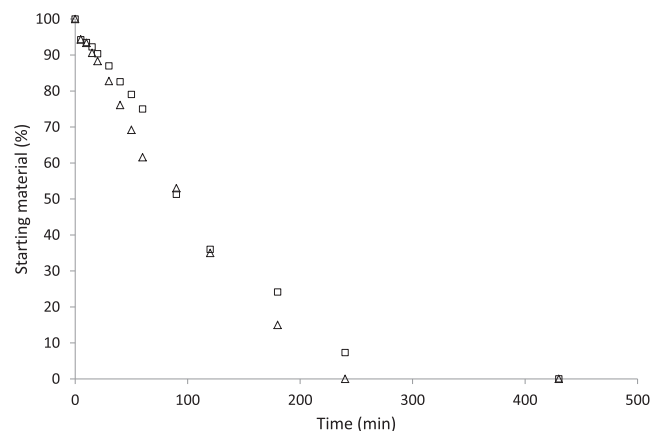
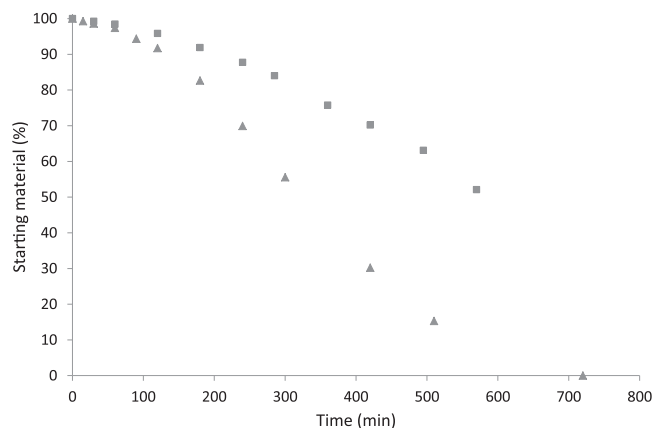
tert-butyl-*N*-Boc-*p*-toluamide (**5j**, Entry 10). To our surprise, neither group was removed at RT and only starting material was observed even after 18 h at 50 °C. Further heating to 80 °C resulted in 39% de-*tert*-butylation to give Boc protected amide **6d**. *N,N*-di-Boc protection is commonly used in organic synthesis¹⁰ and we demonstrate that mono-deprotection of non-amido derivatives is possible (Entry 11), with mild deprotection of the aniline substrate taking place in high yield. Entries 12 and 13 demonstrate an extension to amino acids, with mono-deprotection taking place even in the presence of a *tert*-butyl ester. **6f** and **6g** are obtained in near quantitative yield at rt whilst heating to 50 °C gives no evidence for cleavage of the remaining protecting groups.

We hypothesise the deprotection proceeds via slow release of small quantities of TfOH over the course of the reaction: indeed during the de-*tert*-butylation of **3c**, the pH slowly decreases from pH 7 to pH 5 after 18 h. Repeating the reaction using inert, anhydrous reaction conditions and recrystallised Cu(OTf)₂ gives 45% product after 24 h at rt. This would intimate that limiting the exposure to TfOH acts to reduce the de-*tert*-butylation capacity, reiterating the importance of the triflate observed in Table 1. When the deprotection of **3c** is undertaken in the presence of 10 mol %

NEt₃, no reaction is observed. Exposure of **3c** to 10 mol % TfOH in CH₂Cl₂ produces 100% spectroscopic yield of **4c** after 18 h at rt. However, Boc-deprotection of **5b** using 10 mol % TfOH is less favourable, only producing a 45% spectroscopic yield of **4c**. In terms of handling, the use of an air stable solid such as Cu(OTf)₂ is clearly more attractive than use of TfOH. To reiterate the benefits of Cu(OTf)₂, a comparison of trifluoroacetic acid (TFA) in the deprotection of these substrates does not result in the de-*tert*-butylation of **3c**, with only 10% of **4c** observed after 18 h at rt, similarly no reaction is observed on exposure of **3e** to TFA.

Monitoring the transformation of **3c**, over time appears to show little difference between 5 mol % and 10 mol % loadings (Fig. 2), however the rate of the reaction in the initial stages shows the reaction rate doubles when the loading of Cu(OTf)₂ is doubled (Fig. 4). There is a very rapid initiation period of de-*tert*-butylation, until the first data point is captured after 5 min. De-*tert*-butylation of **3c** is also rapid, with the reaction giving complete conversion to **4c** in 7 h. In comparison the Boc-deprotection of **5b** proceeds more slowly (Fig. 3). However, a first order relationship is also observed between the 5 mol % and 10 mol % catalyst loadings, there is no fast initiation period and initial rates are 0.540 μmol s⁻¹ and 1.046 μmol s⁻¹, respectively.

Further studies are underway, particularly focussing on the unexpected reduced level of reactivity observed with **5j** (Table 3, Entry 10). We are also investigating the extension of the substrate scope beyond simple amides and amino acids to look at the use of the de-*tert*-butylation methodology for synthesis/deprotection strategies of more biologically and pharmaceutically relevant substrates.

**Fig. 2.** Consumption of **3c** with time, varying Cu(OTf)₂ loading (5 mol % ■; 10 mol % ▲). Conditions: **3c** 0.1 M in CH₂Cl₂, RT.**Fig. 3.** Consumption of **5b** with time, varying Cu(OTf)₂ loading (5 mol % ■; 10 mol % ▲). Conditions: **5b** 0.1 M in CH₂Cl₂, rt.

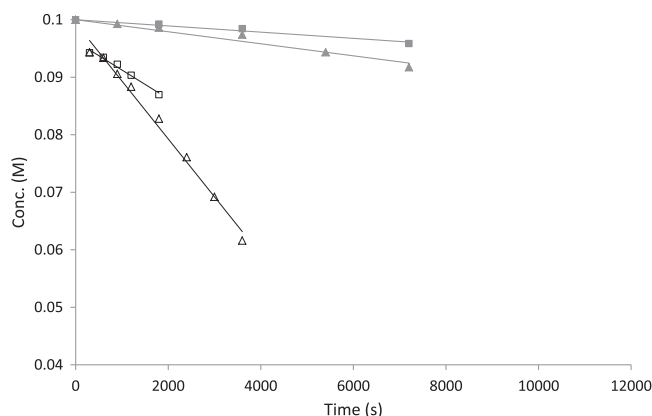


Fig. 4. Comparison of the initial rate of deprotection of **3c** and **5b** with time, varying Cu(OTf)₂ loading. **3c**: 5 mol % Cu(OTf)₂ □, $y = -5.00 \times 10^{-6} + 9.63 \times 10^{-2}x$, $R^2 = 98.1$; 10 mol % Cu(OTf)₂ △, $y = -1.01 \times 10^{-5} + 9.94 \times 10^{-2}x$, $R^2 = 98.9$. **5b**: 5 mol % Cu(OTf)₂ ■, $y = -5.40 \times 10^{-7} + 1.00 \times 10^{-1}x$, $R^2 = 97.3$; 10 mol % Cu(OTf)₂ ▲, $y = -1.05 \times 10^{-6} + 1.00 \times 10^{-1}x$, $R^2 = 95.8$. Conditions: 0.1 M in CH₂Cl₂, rt.

3. Conclusions

We have shown that a catalytic amount of Cu(OTf)₂ can be used to affect a mild de-*tert*-butylation of *N,N*-disubstituted amides. Cu(OTf)₂ proves to be an easily handled and mild reagent for the slow release of TfOH. Alternative sources of strong acid (TFA) fail to de-*tert*-butylate under these reaction conditions and we have shown that the procedure is first order in catalyst and is driven by the release of isobutylene. De-*tert*-butylation is fast and occurs within hours at rt. This protocol can also be used to Boc-deprotect *N,N*-disubstituted amides, di-Boc protected anilines and di-Boc protected amino acids, albeit more slowly. However, Cu(OTf)₂ appears to be a far more favourable reagent for Boc-deprotection both in terms of handling and yield of secondary amide product.

4. Experimental

4.1. General considerations

Reagents were purchased from Sigma Aldrich and used without further purification. Laboratory grade dichloromethane was purchased from Fisher Scientific and used without further purification. The anhydrous test reaction was undertaken using CH₂Cl₂, which had been dried over CaH₂ (reflux), distilled and then degassed using three freeze–pump–thaw cycles. NMR data was collected at 250, 300, 400 or 500 MHz on Bruker instruments in CDCl₃ at 293 K and referenced to residual protic solvent. Room temperature reactions were carried out in 7 mL reaction vials under air in the absence of stirring. Heated and anhydrous reactions were undertaken in Teflon-sealed J-Young reaction tubes. High resolution mass spectrometry (HRMS) analyses were carried out using a Bruker liquid chromatography instrument coupled to an electrospray time-of-flight (ESI-TOF) mass spectrometer.

4.2. Crystal data for C₂₈H₅₂CuF₆N₄O₁₀S₂ (2-Cu)

$M = 846.40$, $\lambda = 0.71073$ Å, monoclinic, space group P2₁/n, $a = 8.2630(1)$, $b = 20.6860(4)$, $c = 11.7690(2)$ Å, $\beta = 106.119(1)^\circ$, $U = 1932.57(5)$ Å³, $Z = 2$, $D_c = 1.455$ g cm⁻³, $\mu = 0.757$ mm⁻¹, $F(000) = 886$. Crystal size = $0.25 \times 0.20 \times 0.20$ mm, unique reflections = 4409 [$R(\text{int}) = 0.0612$], observed reflections [$I > 2\sigma(I)$] = 3455, data/restraints/parameters = 4409/1/243. Observed data; $R1 = 0.0418$, $wR2 = 0.0974$. All data; $R1 = 0.0597$, $wR2 = 0.1072$. Max peak/hole = 0.470 and -0.590 e Å⁻³, respectively. CCDC 990427.

4.3. General method for de-*tert*-butylation and Boc-deprotection

Substrate (0.5 mmol) was added to a reaction vial with CH₂Cl₂ (5 mL) and Cu(OTf)₂ (9 mg, 0.025 mmol, 5 mol %). The reaction was allowed to stand at room temperature for 18 h before being quenched with H₂O and extracted into CH₂Cl₂ (3 × 20 mL). The organic extracts were dried over MgSO₄ and concentrated in vacuo. This yielded the pure product without need for further purification procedures: if pure product was not obtained the reaction was undertaken at 50 °C or 80 °C in a sealed J-Young tube.

4.4. Analysis data for products

Compound **4a**, Table 2, Entry 1. Colourless oil, 71 mg (87%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 7.67 (d, 2H, J 8.2 Hz, ArH), 7.22 (d, 2H, J 8.2 Hz, ArH), 6.24 (br s, 1H, NH), 3.48 (q, 2H, J 7.3 Hz, CH₂CH₃), 2.38 (s, 2H, ArCH₃), 1.24 (t, 3H, J 7.3 Hz, CH₂CH₃); ¹³C NMR (63 MHz; 298 K; CDCl₃) δ 167.4 (C=O), 141.6 (Ar_q), 131.9 (Ar_q), 129.1 (Ar), 126.8 (Ar), 34.8 (CH₂CH₃), 21.4 (ArCH₃), 14.9 (CH₂CH₃); IR (neat) ν 3254, 2974, 1626, 1546, 1509 cm⁻¹. Data matches that of commercial sample (CAS: 26819-08-9).

Compound **4b**, Table 2, Entry 2. White solid, 78 mg (96%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 7.76 (d, 2H, J 7.9 Hz, ArH), 7.49–7.36 (m, 3H, ArH), 6.16 (br s, 1H, NH), 4.26 (septet, 1H, J 6.6 Hz, CH(CH₃)₂), 1.25 (d, 6H, J 6.6 Hz, CH(CH₃)₂); ¹³C NMR (75 MHz; 298 K; CDCl₃) δ 166.7 (C=O), 134.8 (Ar_q), 131.2 (Ar), 128.4 (Ar), 126.8 (Ar), 41.8 (CH(CH₃)₂), 22.7 (CH(CH₃)₂); IR (solid) ν 3297, 2971, 2929, 1631, 1531 cm⁻¹; mp 98–99 °C.¹⁰

Compound **4c**, Table 2, Entry 3. White solid, 72 mg (82%). ¹H NMR (300 MHz; 298 K; CDCl₃) δ 7.65 (d, 2H, J 8.1 Hz, ArH), 7.21 (d, 2H, J 8.1 Hz, ArH), 6.01 (br s, 1H, NH), 4.28 (septet, 1H, J 6.6 Hz, CH(CH₃)₂), 2.39 (s, ArCH₃), 1.25 (d, 6H, J 6.6 Hz, CH(CH₃)₂); ¹³C NMR (63 MHz; 298 K; CDCl₃) δ 166.6 (C=O), 141.6 (Ar_q), 132.0 (Ar_q), 129.1 (Ar), 126.8 (Ar), 41.7 (CH(CH₃)₂), 22.8 (CH(CH₃)₂), 21.4 (ArCH₃); IR (solid) ν 3303, 2973, 1627, 1531 cm⁻¹; mp 99–101 °C. Data matches that of commercial sample (CAS: 2144-17-4).

Compound **4d**, Table 2, Entry 4. White solid, 89 mg (92%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 7.72 (d, 2H, J 8.9 Hz, ArH), 6.90 (d, 2H, J 8.9 Hz, ArH), 5.95 (br s, 1H, NH), 4.26 (septet, 1H, J 6.6 Hz, CH(CH₃)₂), 3.83 (s, OCH₃), 1.25 (d, 6H, J 6.6 Hz, CH(CH₃)₂); ¹³C NMR (63 MHz; 298 K; CDCl₃) δ 166.2 (C=O), 161.9 (Ar_q), 128.5 (Ar), 127.2 (Ar_q), 113.6 (Ar), 55.33 (OCH₃), 41.7 (CH(CH₃)₂), 22.8 (CH(CH₃)₂); IR (solid) ν 3316, 2973, 1606, 1506 cm⁻¹; mp 113 °C. Data matches that of commercial sample (CAS: 7464-44-0).

Compound **4e**, Table 2, Entry 5. White solid, 136 mg (91%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 8.19 (s, 2H, ArH), 7.92 (s, 1H, ArH), 6.89 (d, 1H, J 7.4 Hz, NH), 4.28 (septet, 1H, J 6.6 Hz, CH(CH₃)₂), 1.28 (d, 6H, J 6.6 Hz, CH(CH₃)₂); ¹³C NMR (63 MHz; 298 K; CDCl₃) δ 163.9 (C=O), 136.9 (Ar_q), 131.6 (q, J 34.4 Hz, Ar_q), 127.3 (d, J 3.0 Hz, Ar), 124.3 (app. quintet, J 3.7 Hz, CF₃), 121.6 (Ar), 42.6 (CH(CH₃)₂), 22.6 (CH(CH₃)₂); IR (solid) ν 3292, 3094, 2973, 1640 cm⁻¹; mp 127 °C.¹¹

Compound **4f**, Table 2, Entry 6. White solid, 101 mg (95%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 8.26 (dd, 1H, J 6.5, 2.7 Hz, ArH), 7.89–7.83 (m, 2H, ArH), 7.57–7.37 (m, 4H, ArH), 6.00 (br s, 1H, NH), 4.35 (septet, 1H, J 6.6 Hz, CH(CH₃)₂), 1.28 (d, 6H, J 6.6 Hz, CH(CH₃)₂); ¹³C NMR (75 MHz; 298 K; CDCl₃) δ 168.7 (C=O), 134.8 (Ar_q), 133.5 (Ar_q), 130.2 (Ar), 130.0 (Ar_q), 128.2 (Ar), 126.9 (Ar), 126.3 (Ar), 125.3 (Ar), 124.6 (2Ar), 41.9 (CH(CH₃)₂), 22.7 (CH(CH₃)₂); IR (solid) ν 3286, 2973, 1633, 1529 cm⁻¹; mp 124–125 °C; HRMS (LCMS) 236.1051 (calcd for C₁₄H₁₅NNaO), 236.1068 (obs.).

Compound **4g**, Table 2, Entry 7. Volatile liquid, 55 mg (95%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 5.58 (br s, 1H, NH), 4.08 (septet, 1H, J 6.5 Hz, CH(CH₃)₂), 2.16 (q, 2H, J 7.4 Hz, CH₂CH₃), 1.17 (t, 3H, J 7.4 Hz, CH₂CH₃), 1.14 (d, 6H, J 6.5 Hz, CH(CH₃)₂); ¹³C NMR

(125 MHz; 298 K; CDCl₃) δ 173.6 (C=O), 41.2 (CH(CH₃)₂), 29.8 (CH₂CH₃), 22.7 (CH(CH₃)₂), 9.8 (CH₂CH₃); IR (neat) ν 2972, 1642, 1544 cm⁻¹.¹²

Compound **4h**, Table 2, Entry 8. Colourless oil, 58 mg (74%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 5.63 (br s, 1H, NH), 3.91 (septet, 1H, J 6.6 Hz, CH(CH₃)₂), 2.10 (t, 2H, J 7.3 Hz, C(O)CH₂), 1.65–1.53 (m, 2H, C(O)CH₂CH₂), 1.29–1.25 (m, 4H, CH₂CH₂CH₃), 1.11 (d, 6H, J 6.6 Hz, CH(CH₃)₂), 0.86 (t, 3H, J 6.8 Hz, CH₂CH₃); ¹³C NMR (75 MHz; 298 K; CDCl₃) δ 172.3 (C=O), 41.1 (CH(CH₃)₂), 36.8 (C(O)CH₂), 31.4 (CH₂CH₂CH₃), 25.5 (C(O)CH₂CH₂), 22.7 (CH(CH₃)₂), 22.3 (CH₂CH₃), 13.9 (CH₂CH₃); IR (neat) ν 3075, 2873, 1637 cm⁻¹.¹³

Compound **6a**, Table 3, Entry 6. White solid, 46 mg (94%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 6.78 (br s, 1H, NH), 3.25 (m, 2H, NHCH₂), 2.29 (m, 2H, C(O)CH₂), 1.73 (m, 4H, C(O)CH₂CH₂CH₂); ¹³C NMR (63 MHz; 298 K; CDCl₃) δ 172.9 (C=O), 42.0 (HNCH₂), 31.5 (C(O)CH₂), 22.3, 20.9 (CH₂ alkyl); IR (solid) ν 3190, 2936, 1668 cm⁻¹. Data matches that of commercial sample (CAS: 675-20-7).

Compound **4k**, Table 3, Entry 7. White solid, 54 mg (95%). ¹H NMR (400 MHz; 298 K; CDCl₃) δ 6.56 (br s, 1H, NH), 3.21 (m, 2H, NHCH₂), 2.47 (m, 2H, C(O)CH₂), 1.77–1.43 (m, 6H, C(O)CH₂CH₂CH₂CH₂); ¹³C NMR (63 MHz; 298 K; CDCl₃) δ 175.2 (C=O), 45.7 (HNCH₂), 39.0 (C(O)CH₂), 28.7, 28.2, 23.1 (CH₂ alkyl); IR (solid) ν 3195, 2928, 1652 cm⁻¹. Data matches that of commercial sample (CAS: 105-60-2).

Compound **6b**, Table 3, Entry 8. White solid, 34 mg (54%). ¹H NMR (400 MHz; 298 K; CDCl₃) δ 6.72 (br s, 1H, NH), 3.31–3.23 (m, 2H, NHCH₂), 2.37 (m, 2H, C(O)CH₂), 1.76–1.53 (m, 2H, C(O)CH₂CH₂CH₂CH₂CH₂); ¹³C NMR (63 MHz; 298 K; CDCl₃) δ 177.9 (C=O), 41.81 (NHCH₂), 32.18, 27.98, 25.67, 24.38 (CH₂ alkyl); IR (solid) ν 3226, 2923, 1647 cm⁻¹. Data matches that of commercial sample (CAS: 673-66-5).

Compound **6c**, Table 3, Entry 9. White solid, 61 mg (83%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 9.50 (br s, 1H, NH), 7.17–6.86 (m, 4H, ArH), 2.98 (dd, 2H, J 7.9, 7.1 Hz, C(O)CH₂CH₂), 2.65 (dd, 2H, J 7.9, 7.1 Hz, C(O)CH₂CH₂); ¹³C NMR (75 MHz; 298 K; CDCl₃) δ 172.5 (C=O), 137.2 (Ar_q), 127.8 (Ar), 127.4 (Ar), 123.5 (Ar_q), 122.9 (Ar), 115.6 (Ar), 30.6 (C(O)CH₂), 27.6 (C(O)CH₂CH₂). Data matches that of commercial sample (CAS: 553-03-7).

Compound **6d**, Table 3, Entry 10. White solid, 45 mg (39%). ¹H NMR (300 MHz; 298 K; CDCl₃) δ 7.61 (d, 2H, J 8.3 Hz, ArH), 7.19 (d, 2H, J 8.3 Hz, ArH), 5.97 (br s, 1H, NH), 2.37 (s, 3H, ArCH₃), 1.46 (s, 9H, C(CH₃)₃); ¹³C NMR (63 MHz; 298 K; CDCl₃) δ 165.5 (C=O_{amide}), 150.6 (C=O_{Boc}), 141.2 (Ar_q), 129.5 (Ar), 128.0 (Ar_q), 127.6 (Ar), 82.6 (C(CH₃)₃), 27.9 (C(CH₃)₃), 21.6 (ArCH₃); IR (solid) ν 3150, 2990, 1752, 1659 cm⁻¹; mp 130 °C.¹⁴

Compound **6e**, Table 3, Entry 11. Colourless oil, 85 mg (82%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 7.16 (d, 2H, J 9.2 Hz, ArH), 7.00 (d, 2H, J 9.2 Hz, ArH), 6.41 (br s, 1H, NH), 2.21 (s, 3H, ArCH₃), 1.43 (s, 9H, C(CH₃)₃); ¹³C NMR (63 MHz; 298 K; CDCl₃) δ 152.9 (C=O), 135.7 (Ar_q), 132.4 (Ar_q), 129.4 (Ar), 118.7 (Ar), 80.2 (C(CH₃)₃), 28.3 (C(CH₃)₃), 20.6 (ArCH₃); IR (neat) ν 3287, 3131, 2966, 1685 cm⁻¹.¹⁵

Compound **6f**, Table 3, Entry 12. Colourless oil, 129 mg (90%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 4.91 (d, 1H, J 8.2 Hz, NH), 4.15 (app. q, 1H, J 8.2 Hz, CH₂CH), 1.68 (septet, 1H, J 6.5 Hz, CH(CH₃)₂), 1.43 (s, 11H, CH₂CH & C(CH₃)₃), 1.41 (s, 9H, C(CH₃)₃), 0.92 (d, 6H, J 6.5 Hz, CH(CH₃)₂); ¹³C NMR (63 MHz; 298 K; CDCl₃) δ 172.6 (C=O_{ester}), 155.3 (C=O_{Boc}), 81.3 (C(CH₃)₃ ester), 79.4 (C(CH₃)₃ Boc), 52.6 (CH₂CH), 42.0 (CH₂CH), 28.2 (C(CH₃)₃), 27.9 (C(CH₃)₃), 24.7 (CH(CH₃)₂), 22.0 (CH(CH₃)₂); IR (neat) ν 2960, 1713, 1501, 1455, 1366 cm⁻¹; HRMS (LCMS) 310.1994 (calcd for C₁₅H₂₉NNaO₄), 310.1985 (obs.).

Compound **6g**, Table 3, Entry 13. Colourless oil, 155 mg (96%). ¹H NMR (250 MHz; 298 K; CDCl₃) δ 7.37–7.21 (m, 5H, ArH), 5.09 (d, 1H, J 7.9 Hz, NH), 4.50 (app. q, 1H, J 7.90 Hz, CH₂CH), 3.10 (d, 2H, J 7.90 Hz, CH₂CH), 1.47 (s, 9H, C(CH₃)₃ ester), 1.44 (s, 9H, C(CH₃)₃

Boc); ¹³C NMR (63 MHz; 298 K; CDCl₃) δ 170.9 (C=O_{ester}), 155.0 (C=O_{Boc}), 136.3 (Ar_q), 129.4 (Ar), 128.2 (Ar), 126.7 (Ar), 81.8 (C(CH₃)₃ ester), 79.5 (C(CH₃)₃ Boc), 54.8 (CH₂CH), 38.9 (CH₂CH), 28.2 (C(CH₃)₃), 27.8 (C(CH₃)₃); IR (neat) ν 2977, 2929, 1712, 1496, 1455, 1366 cm⁻¹.¹⁶

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Supplementary data

Supplementary data contains experimental details, full spectroscopic analysis data and crystallographic data. Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.tet.2014.07.080>.

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